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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,741	12/10/2003	Thomas M. Schmitt	2223-171	5362

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EXAMINER	
LIETO, LOUIS D	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/731,741	SCHMITT ET AL.	
	Examiner	Art Unit	
	Louis D. Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,8,10-28 and 44-49* is/are pending in the application.

4a) Of the above claim(s) *18-21,23-28 and 47-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,8,10-17, 22 and 44-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/28/05 has been entered.

Applicant's response filed on 1/26/2006 is acknowledged. Claims 1,2,4,8,10-28 and 44-49 are pending in the instant application. Applicant canceled claims 29-43, amended claim 1 and added claims 44-49. Claims 18-21 and 23-28 remain withdrawn.

Newly submitted claims 47-49 are directed to an invention that is independent or distinct from the invention originally elected for the following reasons: The claims are drawn to a method of forming TCR-$\alpha\beta^+$ $CD4^+$ $CD8^-$ cells *in vivo*. The claims involve the patentably distinct step of administering T cell lineage cells to a recipient animal with a thymus. Therefore claims 47-49 are directed to a method of *in vivo* T cell lymphopoiesis. The original elected invention was directed to an *in vitro* system comprising a notch ligand that supports T cell lymphopoiesis, and a method of using the system to form cells of the T cell lineage. New claims 47-49 are drawn to patentably distinct subject matter that is different from the originally elected group.

Accordingly, claims 47-49 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1,2,4,8,10-17, 22 and 44-46 are currently under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1,2,4,8,10-17, 22 and 44-46 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims have been amended so that they now contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The original disclosure fails to recite the negative limitation of "wherein the T cells produced are not TCR-$\alpha\beta^+$ $CD4^+$ $CD8^-$" (Claim 1). Applicants have not indicated where in the specification **implicit or explicit** support for this negative limitation can be found. Based on the disclosure as filed a practitioner in the art would not be able to determine that the inventors contemplated the negative limitation of "wherein the T cells produced are not TCR-$\alpha\beta^+$ $CD4^+$ $CD8^-$" at the time of filing. Further, a key word search of the specification fails to find disclosure of these limitations anywhere in the specification as initially filed. Therefore, since the specification as filed doe not contain support for the term "wherein the T cells produced are not TCR-$\alpha\beta^+$ $CD4^+$ $CD8^-$" it is considered to be new matter. See M.P.E.P. 608.04(a). Claims 2,4,8,10-17, 22 and 44-46 depend from claim 1.

The rejection of claims 1,2,4,8,10-17, 22, 24 under 35 U.S.C. 112, first paragraph, because the specification is withdrawn in view of applicant's amendment to claim 1. However,

applicant is cautioned that said amendment has been determined to be new matter, see above and may be reinstated in view of any future claim amendments.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 1,2,4,8,10-17, 22, 24 and 29-43 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements, is withdrawn in view of applicant's amendments to the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1,2,4,8 and 12-15, 17, 22, and 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jaleco et al. {Jaleco et al. (2001) J. Exp. Med. 194:991-1001}, in view of Nakano et al. {Nakano et al. (1994) Science 265:5175} and Tatsumi et al. {Tatsumi et al. (1990) Proc. Natl. Acad. Sci. 87:2750-2754}. This new rejection is necessitated by applicant's amendments to the claims, and addition of new claims.

Jaleco et al. provides guidance on an *in vitro* system comprising stromal cells expressing the Delta-1 ligand, which supports T cell lymphopoiesis of human hematopoietic progenitor cells (HPCs) but does not support B cell lymphopoiesis (Abstract). Specifically, Jaleco et al. teaches

that culturing HPCs with mouse S-17 stromal cells that express Delta-1, wich inhibits B cell differentiation and produces $CD3^+$ $CD4^+$ $CD8^+$ T cells (pg. 992, col. 1, pgph 3; pg. 992, Materials and Methods; pg. 995, Table 1). Abbas et al. teaches that T cells that are $CD3^+$ $CD4^+$ $CD8^+$ have inherently undergone TCR V(D)J rearrangement {Abbas et al., (1994) Cellular and Molecular Immunology 2nd ed., 1-457; pg. 176, Fig. 8-5; pg.178 col. 1}. Jaleco et al. teaches that transfecting S-17 stromal cells specifically blocks B cell lymphopoiesis (Abstract). Further, Jaleco et al. teaches that the immature T cells were separated from the aggregate population of cells (pg. 995, Table 1). Jaleco et al. does not teach using OP-9 stromal cells or inducing lymphopoiesis in mouse cells.

Nakano et al. supplements the guidance of Jaleco et al. by teaching the use of mouse OP-9 stromal cells (which inherently does not express M-CSF) to generate lymphohematopoietic cells (Abstract). Nakano et al. teaches that it is advantageous to use stromal cells lacking M-CSF when studying lymphopoiesis because the presence of M-CSF can inhibit the differentiation of ES cells to blood cells other than macrophages.

Tatsumi et al supplements the guidance of Jaleco et al. by teaching an *in vitro* system for studying the differentiation of mature mouse T cells from CD3- CD4-CD8- precursors by culturing them with mouse stromal cells (Abstract; pg. 2750, Materials and Methods).

Based on the guidance provided by Jaleco et al. on an *in vitro* system comprising stromal cells the Delta-1 ligand, which supports T cell lymphopoiesis of HPCs but does not support B cell lymphopoiesis and the teachings of Nakano et al. on the advantages of using OP-9 cells when studying lymphopoiesis, it would be *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Jaleco et al. by replacing

the mouse S-17 stromal cells with OP-9 cells. Further it would be *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to use the assay system of Jaleco et al. with the OP-9 cells of Nakano et al. to study mouse T cell differentiation with the mouse precursor cells using the precursors taught by Tatsumi et al.

A practitioner in the art would be motivated to modify the method of Jaleco et al. with the OP-9 cells of Nakano et al. in order to reduce the number of inhibitory ligands and to optimize T cell induction. Further the practitioner would be motivated to use this system to study mouse T cell lymphopoiesis in order to optimize the number of T cells and variety of sub-types induced.

The person of ordinary skill in the art would have a reasonable expectation of success because the modifying the teachings of Jaleco et al. by replacing the S-17 stromal cells with the OP-9 cells of Nakano et al. would have been a routine modification in the art at the time of filing. Further, the use of mouse hematopoietic precursor cells, such as those taught by Tatsumi et al. , instead of human hematopoietic precursors would have been a routine modification in the art at the time of filing.

Response to Arguments

Applicant's arguments filed 11/28/05 have been fully considered but they are not persuasive. Applicant argues that the cited references do not teach a system for the generation of mature T cells. Applicant is arguing limitations that are not present in the claims. The claims are drawn to an *in vitro* system that supports T cell lymphopoiesis. T cell lymphopoiesis includes all precursor, immature and mature T cells, as recognized by the specification (pg. 19, lines 5-15).

Jaleco et al. teaches an *in vitro* system to produce $CD3^+$ $CD4^+$ $CD8^+$ T cells (pg. 992, col. 1, pgph 3; pg. 992, Materials and Methods; pg. 995, Table 1). Therefore Jaleco et al. teaches an *in vitro* system supports T cell lymphopoiesis.

Next applicant argues that the cited references do not teach a system that uses modified OP9 cells to generate mature T cells. Applicant then argues that each reference does not teach modified OP9 cells.

It appears that Applicant is arguing that the cited references do not expressly suggest the claimed invention. However, it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Burkel, 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors. It also appears that applicant is attempting to attack each reference individually. However, in a 103 rejection the references must be considered as a whole.

Next applicant argues that none of the references teach using DL-1 or DL-4 to generate mature T-cells. However, as stated above applicant is arguing limitations that are not present in the claims. The claims are drawn to an *in vitro* system that supports T cell lymphopoiesis.

Next applicant argues that the cited references do not teach a system for T cell expansion. It is noted that claim 22 does not limit the invention to a particular range of expansion. Therefore the lower cellular expansion recognized by applicant (Reply pg. 13, pgph 4) meets this limitation.

Next applicant argues that there was no motivation for one of ordinary skill in the art to

modify the teachings of Jaleco. It is again noted that the claims are drawn to an *in vitro* system that supports T cell lymphopoiesis, not to mature T cells. The practitioner would be motivated to use the OP-9 cells taught by Nakano et al because the presence of M-CSF can inhibit the differentiation of ES cells to blood cells other than macrophages. At a minimum a practitioner practicing the teachings of Jaleco would be motivated to use the OP-9 cells in order to optimize T cell induction and decrease the production of macrophages. This would be especially relevant when studying mouse T cell lymphopoiesis in order to optimize the number of T cells and variety of sub-types induced.

Applicant's arguments focus on each reference individually. However, the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. In re Nilssen, 7 USPQ2d 1500 (Fed. Cir. 1988).

Next applicant argues that there is no reasonable expectation of success. Applicant argues that the Nakano system required modifications before it was able to support effective T cell differentiation using OP-9 cells expressing DL-1. However, Nakano does not stand alone, but is part of a larger multi-reference rejection. The teachings of the references must be considered together. Next applicant argues that the inventors used 99% pure CD34+ cells in the claimed invention, while Jaleco only used 95% pure Cd34+ cells. It is noted that this limitation is not present in the claim. Further, applicant has not explained why the system taught by Jaleco would not be optimized by the use of OP-9 stromal cells. Based on the results achieved by Jaleco and

the teachings in the supporting references, a practitioner in the art would have a reasonable expectation of success because replacing the S-17 stromal cells with OP-9 cells would have been a routine modification in the art at the time of filing. It is noted that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See In re O'Farrell, 7 USPQ2d 1673 (CAFC 1988).

Next applicant argues that the *in vitro* production of mature T cells fulfills a long-felt need in the art. However, it is again noted that the claims are drawn to an *in vitro* system that supports T cell lymphopoiesis, not to mature T cells. Given the prior teachings in the art, as set forth above and in the office actions of 1/25/05, the broadly claimed invention is obvious.

Applicant would be successful in overcoming the above art rejection if they limited the claims to a method of producing mature T cells.

No claims allowed

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business

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